



The Academy of
Medical Sciences

Microbial Challenge Studies of Human Volunteers



*A guidance document from the
Academy of Medical Sciences*

July 2005

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Vaccination, injection preparation and
malarial carrying mosquito

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Summary and recommendations

The Academy of Medical Sciences convened a Working Group to consider research on microbial challenge studies of human volunteers: the deliberate infection of human volunteers with micro-organisms. Historically such studies have contributed uniquely to our understanding of pathogenesis, immune responses, and the treatment and prevention of microbial diseases, such as influenza, hepatitis and cholera. These studies may furnish proof-of-concept for a therapeutic intervention, significantly reduce the time required to realise key milestones in vaccine development and accelerate progress towards phase III trials.

The Academy recognises that, despite the importance and proven utility of such studies, this form of clinical investigation raises a number of issues that merit special consideration:

- the deliberate exposure of humans to living microbes and therefore the potential for healthy people to develop a disease
- the clinical research protocols, such as those designed to investigate the natural history of infection, that are not covered by the European Clinical Trials Directive (ECTD) implemented in the UK as the Medicines for Human Use (Clinical Trials) Regulations in May 2004.

The Academy recognises the important ethical, safety, legal and societal consequences of this type of research and the need for researchers to ensure that appropriate and adequate preparation is undertaken with regard to the following:

- transparency and accountability, including protocols, training, trial conduct, safety monitoring procedures and the reporting of adverse events
- procedures for the recruitment of volunteers, defining eligibility, compliance, assessing competence, provision of information, the avoidance of coercion and conflicts of interest
- ethical and safety considerations, evaluating the concepts of minimal risk of harm and risk assessment
- preparation of microbial challenge materials, including the identification of key elements in quality control

and the necessity for complying with acceptable production standards (Good Manufacturing Practice)

- procedures for consent and confidentiality, including methods for ensuring respect for the autonomy of potential research participants and the use of tissue samples
- indemnity against damages, given the potential for microbial challenge studies to cause injury and to invoke institutional and individual liability.

The Academy considers that the core principles for determining whether such research should, or should not, take place and how such studies should be regulated, are not intrinsically different from other medical research involving human subjects. Specifically, the risks to the safety of participants (both of the enrolled subjects and the broader public) must not be greater than is acceptable in other forms of research. But it is imperative that the standards applied to microbial challenge studies of humans should be of equivalent stringency to those that pertain, for example, to research on drugs.

Recommendation 1: National Expert Advisory Committee

The Academy recommends the formation of a National Expert Advisory Committee (NEAC). The major aim of NEAC is to identify mechanisms to safeguard the safety and welfare of human subjects involved in microbial challenge studies of humans. The aim must be to have in place a framework that is at least as stringent as the scientific, ethical and legal requirements that pertain to, for example, experimental studies of drugs. These aims could be achieved either through identifying a specific role for NEAC itself, or by a broadening of the current remit of existing authorities. One option would be for the NEAC to have mandatory powers of inspection, resourced by fees from the investigator's research support. It should have explicit powers to stop studies for safety reasons, for example through recommending that universities, research councils and major charities withhold requisite indemnity insurance from studies that do not pass inspection.

Thus, the remit of the NEAC would be to:

- provide an expert, independent and representative source of expertise on the relevant scientific, ethical, safety, legal and societal issues relating to microbial challenge studies of humans
- identify, or itself provide, an explicit authority to ensure that microbial challenge studies meet ethical and safety standards that are no less stringent than those of other forms of research involving human subjects
- ensure the proper preparation and storage of microbial challenge materials
- ensure that microbial challenge studies carry adequate indemnity
- establish a central registry of microbial challenge studies
- provide information on adverse events arising from microbial challenge studies and for this information to be in the public domain.

To establish NEAC as a freestanding entity would incur disproportionate administrative costs and might not satisfy public concern for independent oversight of activities that raise safety issues. We therefore suggest that NEAC should be established within an existing organisation.

Recommendation 2: Institutional safety monitoring function

It is proposed that there should be an enhanced level of local safety monitoring of microbial challenge studies. In particular, a suitably qualified local safety monitor should be identified who has the power to stop the study for an individual, on a case-by-case basis, and commence treatment rather than merely stopping recruitment to the study (see Chapter 5).

Chapter one - Introduction

Academy of Medical Sciences initiative

- 1.1 In May 2002, the Academy of Medical Sciences organised a meeting in Oxford to provide a forum for the critical discussion of the risks, benefits and conduct of microbial challenge studies of human volunteers - the deliberate infection of human volunteers with micro-organisms - with particular emphasis on the role of such studies in facilitating research and development of vaccines¹. The consensus of the meeting was that microbial challenge studies have an important contribution to make to our understanding of the natural history of infections and in facilitating research and development of their treatment and prevention.
- 1.2 There is a long history of such studies contributing to knowledge of the aetiology, transmission, treatment and prophylaxis of infectious diseases. A number of considerations were identified at the Oxford meeting that made it expedient to review the current status and future prospects of this research. The impact of microbial diseases on human health continues to be a high public health priority. Increased awareness of emerging or novel diseases, bio-terrorism and escalating resistance to antimicrobial treatments, to cite a few examples, have heightened the need for strengthening relevant research efforts. For example, microbial challenge studies on humans may provide key findings to realise proof-of-concept. These data may significantly reduce the time required to realise key milestones in vaccine development and accelerate progress towards phase III trials. Further, recent advances in microbiology, genomics, immunology and effective treatments allow more information to be obtained from such studies than before and should allow them to be conducted with more detailed monitoring and thus a greater degree of safety.
- 1.3 However, over the past few years a number of concerns have surfaced, especially with regard to

the safety of vaccines. Although many challenge studies, such as those using attenuated organisms or on immune responses, will not be associated with disease, there are some studies in which there is exposure to potentially pathogenic microbes and these will certainly require particularly judicious consideration of the balance between the potential benefits to society and the risks to human volunteers. Thus, it is important that such studies are always carried out so as to conform to the ethical, scientific and safety standards expected of medical research. Institutions and investigators must observe the highest standards of practice; there is a continuing need for appropriate training for those involved, transparency of process and adequate ethical consideration at local, national and international level.

- 1.4 It is also important to consider the circumstances in which, despite potential advances in knowledge, microbial challenge studies may not be appropriate. Scientific knowledge and its interpretation change over time and therefore the criteria for approval of research involving microbial challenge studies of humans must be kept under constant review. To this end, the Working Group recommends the formation of a National Expert Advisory Committee (NEAC), (see Chapter 4). The primary objective of NEAC is to ensure that safety is rigorously monitored.
- 1.5 Following the successful meeting in Oxford, the Academy, drawing upon the wide-ranging clinical and laboratory expertise of its members and a number of expert colleagues, appointed a Working Group to pursue some of the outcomes. Specifically the Group was asked to consider the current status of, and future prospects for, microbial challenge studies on human volunteers with the recommendation that the Group's deliberations should be incorporated into a guidance document.

¹ Available from: www.acmedsci.ac.uk/20020522summary.htm Accessed: May 2005

Terms of Reference of the Working Group

- 1.6 • To identify the facets of microbial challenge studies and their implications, that differentiate them from other clinical research using human volunteers.
- To consider the scientific, ethical and legal issues (theory and practice) of conducting microbial challenge studies in human volunteers.
 - To take account of relevant activities by other bodies and to identify the particular value to be added by the Academy of Medical Sciences.
 - To take into account and consider the issues for such studies in the context of existing national, European and international guidelines, with the aim of differentiating challenge studies from other clinical Research and Development (R&D).
 - To consider how to promote and facilitate public accountability and transparency.
 - To compile a guidance document to promote and facilitate high standards in the conduct of microbial challenge studies in human volunteers.

Specific goals and the background for research subject protection

- 1.7 It is the purpose of this document to deliver information and guidance to those in the UK who are interested in the conduct of such studies, particularly, but not exclusively, to professionals already conducting or intending to undertake such studies. It was felt that the document might also be of interest to universities, clinical research institutions and review bodies. A major aim is to build accountability within the research community while conceding and acknowledging the responsibilities of regulatory authorities and ethics committees.
- 1.8 Microbial challenge studies² of humans require special attention because they involve the deliberate exposure of volunteers to live microbes. Although many of these will result in infection, but not disease, some microbes used in challenge

studies are pathogenic and have the potential to cause disease. While microbial challenge studies include some investigations that fall within the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004 which implement the European Clinical Trials Directive (ECTD), other investigations clearly do not. The implementation of the ECTD (2001/20/EC) in the UK has broad and important implications for the way in which studies using human subjects will be conducted³.

- 1.9 On the basis of this and other discussions, it would appear that some investigational studies, including some microbial challenge studies, are not covered by the Regulations, even if they involve use of an existing or potential medicinal product, if the study does not specifically aim to ascertain the efficacy or safety of that product. Thus, in addition to their value in investigating the protective potential afforded by vaccines, microbial challenge studies not covered by the Regulations may be designed to investigate the pathogenesis of infections, research of great importance, especially for microbes that are obligate for humans. For example, microbial challenge studies can provide essential information on the factors involved in establishing colonisation, its duration and the induction of local and systemic immune responses, data that cannot be obtained through other means of investigation.
- 1.10 Although this guidance document focuses on the UK, it is appreciated that there may be compelling scientific reasons for carrying out research in developing countries and that special considerations may apply (see Chapter 4 for further discussion).
- 1.11 Microbial challenge studies involve the introduction of live organisms into human subjects, a procedure that may raise specific ethical and procedural issues. It is therefore important to consider diligently whether there are differences between microbial challenge studies of humans and other research such as that involving medicinal products. The Working Group concluded that society would not want to forfeit the benefits of research that could provide major and unique scientific advances, but equally it was incumbent

² The remit of the Working Party was confined to the use of live organisms and specifically excludes consideration of killed organisms or components derived from them.

³ A detailed discussion of the issues has been published by the Academy (Academy of Medical Sciences, 2003).

upon the research community to be accountable and to have considered deeply the implications of such studies, weighing the balance of benefit and risk, in a fashion that was transparent and open to public review.

1.12 These considerations are complex since some studies may involve risk even when every precaution is taken and this must be recognised. It is reasonable to consider the ethical issue of what rights should be accorded an individual who wishes to participate in research that has substantial potential benefits to society. To what extent does altruism, or the 'feel-good' factor of the volunteer, balance the risk which society might allow, assuming that it is not too extreme?

1.13 Nonetheless, it is also evident that protection of research participants must be a paramount consideration involving a range of safety protection preconditions (Institute of Medicine, 2003):

- comprehensive review of protocols, including risk assessment
- ethical participant-investigator interaction
- risk-appropriate safety monitoring
- quality assurance.

1.14 The publication from the U.S. Institute of Medicine (2003) describes in detail the effective mechanisms that should be in place to protect human participants in research studies: these studies should be conducted in an environment that emphasises accountability, ensures adequate resources for protection, provides ethics education to those conducting and overseeing the research, and seeks transparent dialogue with all involved. In addition to the detailed coverage provided by the Institute of Medicine, further information on the generic issues for clinical research studies can be found in standard textbooks⁴, and some of these considerations are listed in Appendix 1.

1.15 There may need to be a greater effort to provide information to the public about challenge studies of human volunteers than has been the case for other clinical studies. Public confidence in

biomedical research is fragile and the deliberate use of infectious agents in microbial challenge studies of volunteers is likely to engender specific concerns, despite the benefits to the public of such studies and the paucity of documented evidence of unacceptable harm in such studies conducted over many years. The Working Group was unaware of any reliable quantitative estimate of the number of adverse events related to participation in microbial challenge studies overall or, indeed, a collective record of all those who participate, either in the UK or other countries such as the US. Thus, if there is to be transparent and accountable behaviour on the part of researchers, information on the outcome from these studies needs to be widely available.

1.16 Collection of data to define the clinical research risk numerator and denominator on an annual basis would be an important step in compiling the evidence base to measure advances in research subject protection. Further, as a first step, the Working Group considered that a central national registry of all microbial challenge studies could be initiated (see Summary and recommendations). The provision of this information by the research community would serve to emphasise the importance of this research and stimulate informed discussion.

1.17 The purpose of this document is to guide and facilitate microbial challenge studies in humans, but is not intended to be prescriptive. Nonetheless, such research must comply with the principles of good clinical and research practice. In this regard, reference is made throughout to the relevant regulations and advice provided by other bodies; a list of source material is provided as the current evidence base from which to apply the specific guidance for microbial challenge studies as part of the UK implementation of the ECTD (see Appendix 6). While space does not permit full discussion here of the underlying ethical principles and procedures relevant to clinical research, a brief outline is provided to serve as background to the practical considerations relating to microbial challenge studies.

⁴ For example, Kennedy & Grub, 2000; Beauchamp & Childress, 2001; McGuire & Chadwick, 2002

General ethical framework for medical research in the UK

1.18 Ethical considerations concerning research involving human subjects highlight four main issues:

- respect for the autonomy of the potential participants
- the risk of harm
- the value of the research
- and aspects of justice.

1.19 The Declaration of Helsinki (WMA, 2000) stipulates that the use of humans for research should be reviewed by a properly constituted ethics committee. Many countries now have regulations governing the formation and procedure of research ethics committees. Some, for example the Netherlands, Belgium and US already have specific legislation in this area; others, such as the UK, currently have a regulatory system controlled by government but not legislation.

1.20 In the UK, there are two main types of research ethics committees: Local Research Ethics Committees (LRECs) and Multicentre Research Ethics Committees (MRECs). Deciding which committee is relevant will depend on the geographical spread of the research⁵. The independence of research ethics committees from the researchers and sponsors of research is seen as a fundamental criterion of research governance.

Good Clinical Practice

1.21 The requirement of international drug regulatory agencies for the protection of research participants and for obtaining good quality data on efficacy and safety has led to the development of detailed guidance for the conduct of clinical trials of new drugs. These are codified in national and international legislation and summarised in the International Conference on Harmonisation (ICH) E6 document which defines Good Clinical Practice (GCP). While many of the details of GCP may not be directly relevant to challenge studies, the concept - with the goal of generating the highest quality data possible while safeguarding participant rights and safety - is highly relevant to a microbial challenge study. For this reason, and the likelihood that such guidelines would be referred to by legal and regulatory authorities as a benchmark, researchers who conduct microbial challenge studies should be familiar with GCP and seek to implement it where appropriate to the context of their study.

⁵ Further information can be found on the Central Office for Research Ethics Committees (COREC) website: www.corec.org.uk.

Chapter two - *Value of challenge studies and historical perspective*

2.1 Human challenge studies with well-characterised micro-organisms provide an opportunity to study many aspects of the course of microbial infection, response to treatment and efficacy of naturally acquired and vaccine-induced immune responses in a manner seldom provided by observations of natural infections. Challenge studies have in the past helped define the causative role of a micro-organism in a disease, for example the role of *Helicobacter pylori* in gastritis (Brzozowski, 2003), and in defining means of transmission. For example, the transmission of yellow fever by mosquitoes was identified in 1900 by microbial challenge with immediate public health impact (reviewed by Chastel, 2003). More recently, molecular analysis of the sequential expression of variant antigens by malaria parasites in deliberately infected volunteers has helped our understanding of a key immune evasion mechanism used by this microbe (Peters *et al.* 2002).

2.2 Challenge studies have provided important information on innate and acquired immune responses and have also contributed to the identification of genetic susceptibility factors for infectious diseases (McCool *et al.* 2002). Challenge research is also valuable in investigating the acceptability and safety of vaccines. Thus, in assessing protection, the value of challenge research lies in several areas. First, protection against a defined drug sensitive strain of microbe can be evaluated in a controlled setting. Secondly, potential efficacy of a vaccine or drug can be assessed in a smaller number of volunteers and more rapidly than through natural exposure. Thirdly, the contribution of many biomarkers to resistance and protection against infection, such as various vaccine-induced immune responses, can be assessed relatively efficiently. For example, deliberate colonisation of human volunteers with pneumococci has allowed a detailed investigation of the local and systemic immune responses to specific proteins that are potential vaccine candidates (McCool *et al.* 2002). Similarly, inoculation of volunteers with gonococci (Hamrick *et al.* 2001) has provided a detailed analysis of the variable expression *in vivo* of the microbial antigens during infection.

2.3 In vaccine research, studies on relatively small groups of volunteers can provide compelling evidence that would otherwise require much greater numbers in Phase II-III studies. Without microbial challenge studies of humans, the development of some vaccines would be very much slower. In consequence, a proportion of programmes would not be scientifically or commercially viable. In some circumstances, microbial challenge studies alone have provided sufficient data for licensure, e.g. the genetically modified cholera organism CVD 103 HGR (in Australia and Canada).

History and current status

2.4 There are very strong drivers for medical research: the potential value to society and ultimately to patients, the quest for scientific understanding, and economic and commercial interests. Because these drivers for research can be so strong it is important that all proposed research is carefully scrutinized from an ethical perspective. The history of medical research provides many examples of ethically problematic research, including microbial challenge studies (Brody, 1998). Two key issues for the scrutiny of such research studies are whether they put those participating in the research at an unacceptable level of risk and whether they were carried out without adequate consent.

2.5 Microbial challenge studies of human volunteers have a history of more than 200 years since the first recorded challenge of a vaccinated child with virulent smallpox virus by Edward Jenner. They have played an important role in medical research, analysing disease course and pathogenesis, assessing drug and vaccine efficacy. Examples of studies using microbial pathogens are set out below:

2.6 Enteric pathogens: Challenge studies with cholera bacilli, *Salmonella typhi* and enterotoxigenic *Escherichia coli* have been used in the evaluation of novel vaccines against these pathogens at the Centre for Vaccine Development, University of Maryland, Baltimore.

- 2.7 Hepatitis viruses: Formal proof of the mode of transmission of hepatitis E virus was provided by oral self-infection (Chauhan *et al.* 2003) and the natural history of hepatitis B infection by exposure of children to infectious material (Ward *et al.* 1958; Krugman, 1986).
- 2.8 Influenza and common cold: From 1946 to 1989 the Medical Research Council Common Cold Research unit at Salisbury undertook challenge studies of volunteers that made numerous contributions to the understanding of the microbiology, immunology, transmission and pathogenesis of these viral infections (Hendley and Gwaltney, 1988) as well as to vaccine development against influenza. Challenge studies with influenza A strains have been undertaken to assess both vaccines and antiviral drugs (Jennings *et al.* 1978; Hayden *et al.* 1999).
- 2.9 Malaria: Before the availability of effective antibiotics to treat syphilis, it was discovered that the induction of fever by malaria infections was sometimes effective at alleviating neurosyphilis. The 1927 Nobel Prize was awarded to Wagner Jauregg for this discovery. Such 'malaria therapy' was used widely in many European countries including the UK until the late 1930s. Subsequently, induced malaria infections have been used for evaluation of anti-malaria drugs and, more recently, in vaccine development (Church *et al.* 1997). The malaria challenge protocol currently used in the UK was developed in the USA where several hundred volunteers had been challenged safely before it was used in the UK for the first time in 1999. These challenges are usually undertaken by bites of infectious laboratory-reared mosquitoes with a laboratory strain of parasite, but blood-stage parasite challenge is also employed. *Plasmodium falciparum* is the usual parasite studied but *Plasmodium vivax* has also been reported. Vaccine related challenge studies are currently in progress in the UK.
- 2.10 Pneumococcus: Challenge studies have been reported to assess immunological correlates of protection against nasopharyngeal colonization of *Streptococcus pneumoniae* (McCool *et al.* 2002).
- 2.11 Others: Infectious agents that were evaluated, mostly in early studies, included anthrax, gonococcus, tularaemia, Q fever and plague (Rosenbaum and Sepkowitz, 2002). Phase I/II trials of attenuated live vaccines are essentially microbial challenge experiments (Gans *et al.* 1988; Marchant *et al.*, 1999)
- 2.12 These examples of research involving human volunteers expose both their scientific utility and ethical complexity. They raise a number of issues that need to be considered in the future design of human microbial challenge studies, especially relating to safety and the accountability of investigators. In particular, and without making judgements on the complexity of the ethics of studies that took place centuries (Jenner), or decades ago (hepatitis B), it is also clear that contemporary opinion would consider some of these studies to be unethical. In this respect, the Working Group noted that there is a distinction between ethical issues that relate to process (e.g. the adequacy of seeking informed consent) from those that determine what may constitute an acceptable risk of harm even if consent is obtained.
- 2.13 In the view of the Working Group, the consent procedures, and level of risk of harm that competent informed volunteers should take, should be the same for Challenge Studies as for other areas of medical research. For many microbes, particularly obligate human pathogens such as *Streptococcus pneumoniae* or *Plasmodium falciparum*, microbial challenge of humans represents the only definitive source of biologically relevant data to guide the natural history of the infection and the potential protective effects of candidate vaccines under development. However, it should be noted that a new Food and Drugs Administration (FDA) rule introduced in 2002 now permits the submission of animal data to demonstrate the efficacy of new drugs and biological products when human efficacy studies are not ethical or feasible (FDA, 2002). One current application is the study of anthrax vaccines (e.g. challenge studies in non-human primates, Institute of Medicine 2002). Endeavours to accelerate vaccine research and development in response to the threats of bio-terrorism may begin to impact more broadly on the scientific and regulatory framework for challenge studies.

Chapter three - *Conduct of clinical trials: overview*

- 3.1 All challenge protocols should undergo independent and rigorous peer review to assess scientific quality, the importance of the research to increase knowledge, and the appropriateness of the study methodology to answer the questions posed. Scientific review feeds into the ethical review process and it is important that the scientific peer review process is sufficiently informed about the specific considerations relating to microbial challenge studies. It is important to ensure that the laboratory and clinical data are published, whether 'positive' or 'negative' (in terms of the original purpose of the trial) so that it is not necessary to repeat experiments, at least without knowing what previous studies showed.
- 3.2 It is critical to establish whether a research proposal involving microbial challenge of humans falls within or outside the remit of the ECTD. If outside, it will be judged, at least within a legal context, according to common law and best practice. It is the responsibility of the researcher to decide this, and to seek appropriate guidance. This guidance document does not provide the basis for making this decision. This is one area in which the introduction of an advisory oversight process could be a valuable resource (see Summary and recommendations).
- 3.3 Among the practical points to consider at scientific review, some of which will be considered in further detail subsequently as they also relate to safety considerations, are:
- 3.4 Scientific merit. Does the scientific information that is likely to be obtained justify the risk? How does the study compare with any previous similar trials?
- 3.5 Alternatives to challenge studies. What other means are available for obtaining the answer sought on vaccine or drug efficacy or pathogenesis? What are the relative merits of the various possible study designs?
- 3.6 Ethical review. Has ethical approval already been obtained? If not, is this likely to be forthcoming?
- Will the review body be capable of assessing the ethical and scientific issues or might specialist advice be required? Is the study to be reviewed by a regulatory authority as well as by an ethics committee? Has the local ethics committee sufficient scientific expertise?
- 3.7 Study design. What is the study design? Are the investigators/subjects blinded to the intervention under assessment? How are subjects to be recruited, randomised or matched? Is the study powered to obtain the required information? Will it be possible to recruit the specified number of volunteers without undesirable inducements? Is payment involved? Is there prior experience to guide safety assessment? Is the challenge model previously established or are dose ranging studies required? What is the safety record of the challenge model?
- 3.8 Study conduct and documentation. Will the study conform to GCP regulations? Will the full protocol be reviewed by external advisors or collaborators who may be more familiar with the challenge protocol?
- 3.9 Challenge microbe. Is the strain of microbe used for challenge well-characterised? Is it likely to change with time? Could it increase in virulence? Could an alternative, attenuated pathogen be used? Could host response or pathogenesis differ according to age of the study population? Have tests been done to exclude the possibility of contamination with extraneous agents or toxins?
- 3.10 Monitoring of infection. Are suitable techniques to be used to monitor the infection? Could more sensitive assays be used or developed that would either allow an earlier endpoint to be used to terminate the infection, or more informative safety monitoring? Are there risks to contacts, within or outside the institution, as well as the challenged individual?
- 3.11 Therapy. Is therapy available? What are its adverse effects? Is the proposed therapy suitable? Is treatment failure possible? Will treatment be

directly observed? Are there adequate follow-up procedures to ensure that there is no relapse or recrudescence?

3.12 Trial facilities. Are the local clinical facilities adequate to conduct the study and to deal with possible clinical complications? Are too many volunteers being studied at a time? Is there adequate, appropriately qualified, statistical support for the trial? What facilities are available for record keeping? Is a suitable database available? Will the laboratory assays to be performed be of adequate quality? Are the assays to be used validated or exploratory? If specialised facilities are required to generate the challenge pathogen (e.g. an insectary), are these of adequate standard?

3.13 Staff. Are there sufficient qualified and experienced personnel to undertake the studies. How are their skills and experience recorded, and audited?

3.14 Indemnity. What arrangements have been made for indemnity cover and for compensation of the volunteers?

3.15 Conflicts of interest. Have they been identified, e.g. potential for financial gain? This is a wide-ranging issue and guidance will vary within different institutions.

3.16 Monitoring. What arrangements will be made for study monitoring? Is a local safety monitor identified? Will a data safety and monitoring committee be in place? Is there a risk to the environment? Has the challenge organism the potential to spread to others?

Chapter four - *Ethical considerations*

Issues specific for microbial challenge studies

- 4.1 A major concern about microbial challenge studies derives from the fact that some involve the potential for giving study participants a disease. Many diseases cause very considerable harm to people both in terms of discomfort and risk of long-term serious harm. However, this does not provide grounds against microbial challenge studies if, in fact, the risk of harm is minimal and in line with what is accepted in other types of medical research.
- 4.2 The other reason why giving a disease to a healthy person might be wrong would be if the intention were to cause harm. But in the case of microbial challenge studies, the overall purpose is not to give healthy people disease but rather, for example, to devise an effective vaccine to prevent disease, or for some other goal related to reducing disease and suffering. As a microbial challenge study is closely monitored, definitive intervention can take place early in the infection thus making the risk of diseases much lower than that of natural infection.
- 4.3 The risk of harm in microbial challenge studies will depend on:
- the immunity of the subject
 - the nature and degree of attenuation
 - sensitivity of the challenge organism to antimicrobial treatment, if available, or the extent to which it is self-limiting (control by host defence mechanisms)
 - post-infection monitoring and the purpose of the study.
- 4.4 Researchers must also be clear on the steps to be taken to prevent spread to the community, e.g. the use of antibiotics to ensure termination of carriage/infection (see also Chapter 5). It is noted that recent technical advances may allow microbial challenge studies to be undertaken with a greater level of monitoring and safety than possible previously; for example the use of Polymerase Chain Reaction (PCR) to detect low levels of infection.

- 4.5 Some microbial challenge studies of humans may be perceived as more dangerous than other research but the approach to considering the safety issues should be the same as for any other study:
- define the level of harm and
 - define likely risk of each harm
 - establish what is ethically acceptable in conjunction with research ethics committee review and in the light of the guidelines.
- 4.6 The interests of the participant should be considered at all phases of the research process. There is no simple way to deal with the complex issues so as to lead to a sensible generalisation about minimal risk of harm. It is a consensus judgement, informed by guidelines, ethical committees, investigators and participants. Transparency of principle is paramount. There is no *a priori* reason to assume that microbial challenge studies necessarily present a greater risk of harm than other studies in medical research that are considered to be ethically acceptable.

Quality and value of research

- 4.7 In judging the value and quality of research, the issues for microbial challenge studies of humans are broadly similar to other areas (see also, Hope and McMillan, 2004):
- Is the research itself of good quality? If the aims of the research are trivial or the methodology is poor then it is unlikely to provide future benefit. The Declaration of Helsinki states, 'Medical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature' (s.B11).
 - Is the risk justifiable from the information obtained? Could information be obtained in any other way that exposes participants to less risk?
 - If the research poses some risk of harm to

participants but potential benefit to others in the future, how should these considerations be balanced? The Declaration of Helsinki, and all international and national guidelines, stress that the interests of research participants are given much greater weight than the interests of people in the future who might gain from the research. This is discussed in further detail in Chapter 5.

Risk of harm and medical research

4.8 The Declaration of Helsinki states, 'Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subjects or others'. ICH emphasises that the rights, safety and well being of the study subjects are the most important considerations and should prevail over the interests of science and society (E6 2.3). Identifiable benefits are a necessary, but not sufficient, justification for microbial challenge studies.

4.9 The UK General Medical Council guidelines for medical practitioners state: '...in non-therapeutic research, you must keep the foreseeable risks to participants as low as possible and the potential benefits from the development of treatments and furthering of knowledge must far outweigh any such risks'. This guidance reinforces that important point. Thus, even if the risks of harm were within acceptable limits (and, of course, the participant had given valid consent), the research may be in breach of the guidelines if it could have been carried out more safely.

4.10 In the case of healthy volunteers, what degree of risk of harm, according to the guidelines, is it acceptable for fully informed, healthy, adult volunteers to take? The Royal College of Physicians (RCP, 1996) guidelines have been the most explicit on this point and these guidelines use the concept of minimal risk of harm. There is an important distinction made between two senses of minimal harm - moderate risk of minimal harm and low risk of serious harm. The RCP guidelines also state that, for those circumstances where society rather than the participant may benefit from the research,

however large the benefit, to expose a participant to anything more than minimal risk of harm needs very careful consideration and would rarely be ethical.

4.11 The accepted position on harm to participants in medical research taken by the national and international guidelines may therefore be summarised as follows:

- even though the volunteer is fully informed, competent, not coerced and gives consent, the research could breach guidelines on the grounds that the risk of harm is too great
- however valuable the research, the degree of risk of harm can be no more than 'minimal' (RCP, 1996).

Justice

4.12 Questions of justice are increasingly the focus for ethical discussion in research, particularly with regard to setting inclusion and exclusion criteria. Commonly, women of child bearing age or older people have been excluded from medical research because of the perceived danger of harming the foetus or because elderly people may be at greater risk than younger people from the research or exhibit more background morbidity. The counter argument to this is that the exclusion of particular groups of individuals by virtue of age, gender, health or other factors may deny to those groups the benefits of research as a consequence of their exclusion; for example, microbial challenge studies in children that can provide unique data on age-related issues such as immunogenicity (see also, Chapter 7).

4.13 Nonetheless, UK researchers may be relatively constrained or absolutely required to limit recruitment to subjects who are fluent in English, and such limitation is especially relevant to microbial challenge studies where symptoms or signs may initially be subtle, and could be missed if communication with study staff is difficult. Limiting recruitment in this way, however, could be viewed as discrimination, especially if appropriate alternative staff could be available. Furthermore, disease susceptibility, manifestations and pathology may vary between racial groups.

Certain infections could have a natural target population, which is racially and ethnically different from the population cohort from which a study normally recruits. The primary concern of the investigator in determining the inclusion and exclusion criteria should be the safety of the participants, while taking account of the scientific, ethical and social issues. Any exclusion must receive explicit ethics committee approval and be stated on the information sheet with suitable explanation.

4.14 Recent concern has also arisen about research funded from the richer countries but carried out in developing countries. For example, in randomised controlled trials, should the control arm include best standard care as provided in the richer countries or best standard care as found in the country in which the research proceeds? There has been much debate on this issue in the medical literature as well as discussion by national and international authorities, most recently by the Council for International Organisations of Medical Science (CIOMS) and WMA (Declaration of Helsinki 2000 revisions). It seems reasonable that challenge studies should be encouraged in endemic areas, for there is no need to test every variant of a new vaccine in the developed world before going to a country where the disease is rife. For example, once the safety of a recombinant vaccine has been established the variants could be tested directly in an endemic population.

4.15 However there are real obstacles such as language barriers and low educational levels, different cultural perceptions, fear of perceived exploitation and possible escape of the challenge organism into an environment where vectors are common. This state of affairs seems likely to persist unless, or until, researchers and the relevant Ethics Committees become more proactive. One recent example is afforded by a research team who have initiated debate by asking their local ethical committee whether a measles recombinant vaccine (after safety and efficacy testing in monkeys) might then be investigated through challenge studies in African subjects in the Gambia.

4.16 Thus, although this guidance document focuses on the UK, it is appreciated that there may be good scientific reasons for carrying out the research elsewhere, and that special considerations may apply. In addition to the outputs from WMA and CIOMS, the recent publications from the Nuffield Council on Bioethics (2002) and the European Group on Ethics (2003) are highly relevant in considering these issues further.

4.17 In summary, the Working Group recognises that microbial challenge studies of humans differ overtly from other forms of research in that they involve the deliberate exposure of experimental subjects to potentially pathogenic microbes with the ability to independently multiply and spread. Although this inevitably raises unique concerns, the core principles that determine whether such research should or should not take place, and how such studies should be regulated, are not intrinsically different from other medical research involving human subjects. Specifically, the risks to the safety of participants (both of the enrolled subjects and the broader public) must not be greater than is acceptable in other forms of research. It is imperative that the standards applied to microbial challenge studies of humans should strive to be of equivalent stringency to those that pertain, for example, to research on drugs. The Working Group noted the overall increase in measures to protect the safety of human subjects involved in all forms of clinical trials over recent years and recognised that those relating to microbial products and challenge studies needed to be of equivalent rigour. To this end, it recommends the need for a National Expert Advisory Group (see Summary and recommendations).

Chapter five - *Safety considerations*

Issues to consider for risk assessment

5.1 The investigator needs to consider both the process for risk assessment and the quantification of acceptable risks within the conceptual framework, a framework that may differ from that of other studies. Investigators should perform a formal risk assessment for the proposed challenge study. The format and content of the risk assessment will vary according to the challenge organism and protocol. However, a formal risk assessment is useful to highlight issues that may not have been considered in protocol design, and which may be different for a challenge study than for trials of therapeutic agents. Although many risks cannot be quantified exactly it is helpful to attempt to assign a degree of severity and a likelihood of occurrence. Health and Safety assessment at work requires a formal risk assessment structure, which will require information on the following issues:

- consideration of the predicted properties of the organism to determine if there are any potential mechanisms by which it could represent a hazard to human health
- consideration of the likelihood that, in the event of exposure, accidental or deliberate, the organism could actually cause harm to human health
- consideration of the nature of the work to be undertaken and a detailed review of the control measures to safeguard human health
- the identification of any hazards to the environment (plant, animal, human or physical) and the introduction of any additional control measures to protect the environment.

5.2 The relevant legislation in the UK is different for work with genetically modified organisms (GMOs) and non-GMOs:

For non-GMO work the relevant legislation is: Control of Substances Hazardous to Health Regulations (COSHH) (Health and Safety regulations)

For GMOs the relevant legislation is: The Contained Use and Deliberate Release regulations,

covered by the Scientific Advisory Committee on Genetically Modified Organisms (Contained Use) and the Department of the Environment, Food and Rural Affairs (DEFRA).

- 5.3 The broader environmental issues need to be fully considered even though the risks may be small and there are questions relating to release into the environment that will need to be answered explicitly for GMOs (some of the issues may be generic for non-modified organisms). For example: can the organism get into ground water and hence into water supplies? Can the organism get into animals, particularly those in the food chain? For GMOs, it will be necessary to provide evidence that they enjoy no selective advantage as compared to the wild-type organism.
- 5.4 Before such questions can be answered, initial studies may have to be done in containment, prior to proceeding to outpatients. Thus, specification of the level of containment for a study will depend on the need to amass data to satisfy regulatory agencies, e.g. on virus shedding and fitness relative to wild-type organism, decisions on containment should be monitored on a case-by-case basis. This need to amass data provides further support for the value of a centralised, publicly available data resource.
- 5.5 A formal risk assessment along the lines above provides a valuable opportunity to develop control measures to reduce the risks, and establish monitoring processes to detect the occurrence of any adverse event, especially subtle ones in the workplace, broader environment or to third parties.

Preparation of challenge materials

5.6 In addressing the requirement that research participants should not be put at more than minimal risk of harm, one important specific issue is the quality of materials that are administered in the challenge study. Although discussed here as a safety issue, quality of material is also a scientific issue. The research design will lack merit if the challenge material is poorly controlled or characterised.

- 5.7 In the absence of any specific regulatory framework for human microbial challenge studies, it is theoretically possible that the preparation of challenge agents in academic facilities using seed material, techniques, equipment and reagents could pose a 'greater than minimal risk of harm' to participants. Investigators and ethics committees should recognise that contamination of biological material for challenge studies can occur at different stages in its preparation: for example, during the original isolation of the challenge agent (e.g. nasopharyngeal secretions could be contaminated with retroviruses); during its amplification (e.g. through the use of growth media or primary cell culture that may contain prions, oncogenic viruses etc); through cross-contamination in the production facility; and during its subsequent aliquoting and storage.
- 5.8 Although not a problem limited to challenge organisms (it applies also to all biologicals, including vaccines) potential harms to volunteers from contaminating adventitious agents could become apparent long after the study, possibly years after the apparently safe administration of the challenge agent to many volunteers. Further, consideration must be given to how long a challenge microbe may persist and whether this might pose any potential risk over time. A separate but important issue concerns the possibility of spontaneous changes in the organism during growth *in vitro* (prior to challenge) or *in vivo*. For example, in studies involving challenge with live pneumococci, spontaneous mutations in a surface antigen, PspA, occurred so as to delete portions of the peptide and alter its immunogenicity. Thus, there is clearly a need for full (state of the art) phenotypic and genotypic characterisation of challenge organisms and it may be prudent if in the future they are archived and deposited, for example, in the National Collection of Type Cultures.
- 5.9 Although we are unaware of reports of such adverse events occurring as a result of microbial challenge, it must be admitted that efforts to detect such occurrences may have been inadequate. However, while the risk to volunteers who participate in academic microbial challenge studies is apparently low, the precise risk, in the absence of a formal reporting system and prolonged monitoring, is essentially unknown.
- 5.10 Without formal guidance equivalent to Good Laboratory Practice (GLP), GCP and Good Manufacturing Practice GMP academic researchers were previously faced with a choice of manufacturing challenge agents locally using the best available local resources, or entering into a relationship to obtain a commercially-prepared challenge agent that is prepared to the standards required for vaccine manufacture. Key elements for quality control include:
- well-characterised seed material (sufficient to assure the relevance of any historical data used as part of the supporting risk-benefit analysis)
 - well-characterised cells, if applicable
 - comparative virulence studies (against benchmark reference material)
 - well-characterised and documented growth and maintenance media
 - adequacy of facilities and process comanufacture; consistency of manufacturing process
 - appropriate containment facilities
 - freedom from adventitious agents (including TSEs)
 - identity testing on manufactured material
 - safety testing (animal toxicity studies)
 - batch release tests including infectivity and stability.
- 5.11 Given the difficulties for investigators in meeting these expectations and thus rendering themselves publicly accountable, it is considered essential that the NEAC identifies mechanisms that can provide the authority and resources to commission mandatory evaluation of challenge materials. It is recommended that the NEAC works in conjunction with the Medicines and Healthcare Regulatory Authority (MHRA) and Health and Safety Executive (HSE). Further, universities, research councils and the NHS might withhold indemnity insurance until such approval is obtained.
- 5.12 Financial support for such an authority could be obtained from fees charged to the investigators and become a recognised component of applications for research support grants. However, adequate recognition must be afforded to the problem that many investigators will face the need to provide preliminary data or pilot studies before obtaining grant funding.

5.13 The implementation of the ECTD in the UK through the Medicines for Human Use (Clinical Trials) Regulations 2004 has created pressures for researchers to attain the required standards for investigational medicinal products (manufacturing, characterisation and quality control conditions as specified in article 23 of Commission Directive 91/356/EEC). Detailed guidelines have been published by the European Medicines Evaluation Agency (EMA) for the preparation and control of challenge agents. It would seem advisable that there should be a common standard for preparation of challenge materials whether or not a particular study is covered by the Clinical Trials Directive and irrespective of whether it is conducted in academic facilities. Procedures for human challenge studies, including guidance on the safe preparation, safety testing and archiving of challenge agents, must be in place.

5.14 The Working Group also wished for it to be noted that only a handful of facilities for obtaining GMP materials is available in the UK. There is therefore an urgent need to consider a means whereby a limited increase in the number of such high-standard facilities could be achieved and maintained.

Safety monitoring

5.15 There is a need for an appropriate structure for the oversight of microbial challenge studies with responsibility for patient safety. The key principles for such oversight are safety and independence. The Department of Health and Medical Research Council (MRC) have reviewed monitoring issues as part of the impact assessment and implementation of the ECTD, but the current MRC clinical trial oversight committee structure is not necessarily appropriate or practical for microbial challenge studies.

5.16 It is important to have an independent group to oversee the conduct of all microbial challenge studies, and it is appropriate to document where the ultimate decision for study cessation or continuation lies. It is desirable to introduce additional independent, local responsibility for safety monitoring and control - the power to stop the study for an individual and treat them rather than merely stopping recruitment of new participants (see Summary and recommendations). Empowerment of this local safety monitor raises various practical issues relating to identification and designation of the responsible person and their back up.

Chapter six - *Transparency and accountability*

- 6.1 Before describing some of the specific issues relating to the conduct of microbial challenge studies, further mention will be made of several general requirements that are of great importance, although not specific to microbial challenge studies. These issues are described in the context of the current GCP guidelines from ICH (E6 document) implemented in the UK through the Medicines for Human Use (Clinical Trials) Regulations 2004 and it is recognised that further consideration may be necessary subject to UK implementation of the EU GCP Directive.
- 6.2 Training: (E6 sections 4.1-4.3) ‘The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial... The investigator should have available... sufficient time... an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.’
- 6.3 Transparency and accountability: (E6 section 4.9) ‘The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution... Upon request of the monitor, auditor, LREC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records’.
- 6.4 Serious Adverse Events (SAEs): (E6 section 4.11) ‘All serious adverse events should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator’s Brochure) identifies as not needing immediate reporting. The investigator should also comply with the applicable regulatory requirement(s) relating to the reporting of unexpected serious adverse events to the regulatory authority (ies),’ and the LREC as appropriate (only if under a clinical trials authorisation).
- 6.5 In relating these guidelines to microbial challenge studies it is important, for example, to ensure that the Principal Investigator is qualified and experienced to manage persons infected with the challenge organism under ‘natural’ conditions and that other staff can recognise the early signs and symptoms of pathology. A proper framework for facilities to conduct such studies will be likely to require documented training in GCP. In addition to the importance for safety considerations, these matters are, of course, also important for ensuring the quality of the science undertaken (see Chapter 3).
- 6.6 Resources for monitoring and care must be guaranteed from the study onset and clear arrangements must be in place for the fast transfer of subjects to medical care should they become ill. Transparency and accountability are high priorities with regard to all aspects of challenge studies (e.g. with regard to study staff responsibilities and continuing liaison with GP or other relevant clinicians about subject participation). In the absence of direct legislation, local procedures must be defined in advance between the investigator, REC and sponsor such that SAEs can be efficiently reported, for example to the relevant data and safety monitoring committee and/or ethics committee.

Chapter seven - *Recruitment of volunteers*

- 7.1 Although many safety issues associated with the recruitment of volunteers to microbial challenge studies are broadly similar to other volunteer studies (see Appendix 1 for general points), the investigator should take the following into consideration:
- 7.2 Recruitment procedures: These should be defined in the protocol and reviewed by the relevant ethics committee. Any variation to the approved procedures must receive prior ethical approval by means of a protocol amendment. The locality from which volunteers may be recruited may be limited in outpatient challenge studies.
- 7.3 Inducements and coercion: Advertising should avoid undue emphasis on the amount of financial compensation available to volunteers. As specified by the ICH E6 document (section 3.1), 'The Ethics Committee should review both the amount and method of payment to subjects to ensure that neither presents problems of coercion or undue influence. Payments to a subject should be pro-rated and not wholly contingent on completion of the trial'. What would constitute inducement will depend on local custom and practice. This may be a particularly sensitive issue for microbial challenge studies with regard to the perception of higher risk of harm than other studies. As with other studies, specific power relationships (e.g. academic staff-student) should not be exploited. The doctor-patient relationship is a strong one and particular caution must be taken in those circumstances where a volunteer is recruited via their relationship with medical services. There is also occasional peer pressure on volunteers to participate in challenge studies so whenever volunteers appear to enrol as a group, enquiry should establish that no undue pressure has been exerted. It must be recognised that patients may be fully informed yet unintentionally coerced.
- 7.4 Eligibility: Entry criteria for inclusion in volunteer challenge studies should be at least as strict as for other clinical studies with therapeutic agents in healthy volunteers. Background medical history should be obtained from the volunteer and, whenever possible, from the volunteer's GP or usual physician. GPs should be informed of the subject's inclusion in the study and given contact details of the investigator so that they have the opportunity to raise concerns about participation in the planned study.
- 7.5 Volunteers should not have any newly developed or evolving illness, or be from a population at risk from this, that may adversely affect participation in the study and its interpretation. There should be a clinical examination by an appropriately qualified medical practitioner. Whether to exclude women of childbearing potential, or the use of pregnancy testing/contraception needs to be addressed in the protocol and consent form. Proposals for research on children would have to be considered in terms of guidelines from the Royal College of Paediatrics and Child Health (Hull, 2000).
- 7.6 While it is not the intention of the present guidance to be prescriptive, issues relating to family and community should be assessed. For example, the presence of young children in the family (<2 years old, particularly susceptible to infection) or employment in food handling might be points to be taken into consideration.
- 7.7 In addition, previous exposure to the relevant pathogen and any associated immunity should be evaluated carefully. A full history of participation in other investigational procedures should be taken. Many individuals volunteer serially for various clinical research studies and an exclusion period of six months is often applied between studies. In view of the possibility of cumulative risk from participation in numerous studies, it may be desirable to compile a central registry of volunteers in challenge studies.
- 7.8 Compliance: Safety is often crucially dependent on good compliance and an assessment must be made of the subject's likelihood of complying with the protocol. As much relevant information as possible should be sought. A previous history of mental or psychiatric illness is usually seen as an exclusion criterion. Under most circumstances subjects should be confined until there is evidence

that they are no longer infected. If subjects are not confined during the challenge period, contact details of next of kin and cohabitants should be obtained. Subjects may have travel restrictions imposed during the study to enable close supervision or for regulatory reasons such as prevention of dissemination of a GMO. Such restrictions should be clearly explained and included on the consent form.

7.9 The information provided to the subject should specify what procedures will be followed if the volunteer chooses to withdraw at various stages of the study or fails to comply with the protocol. This information should also indicate that the investigator has the right, after discussion, to terminate the subject's participation if they believe it is in their best interest. If the volunteer decides to cease participation in a study, the subsequent procedures to be adopted will depend on the category of pathogen used. For some named pathogens, public health legislation will determine the imposition of quarantine or other procedures, and the investigator must inform the volunteer of these implications at the time of seeking consent to participate. In contrast, for other organisms there may not be such a statutory requirement but it would seem prudent that, when a subject decides to withdraw from a study, this should be communicated to the public health authorities.

7.10 Provision of other information: The likely clinical consequences of the challenge and the range of clinical responses (particularly, SAEs) should be enumerated and specified in the information sheet for the volunteer, together with details on the approximate number of volunteers who have undergone this procedure locally and globally. The likely impact on work and activities of daily living, and the duration of illness, should also be specified. Appropriate information about animal model toxicity may also be included. Researchers may wish to consider a means to validate that the volunteer has understood the information provided (see Chapter 8).

7.11 The system of protection should be transparent and this will require communication among all parties. Current or potential research participants, acting as full partners in the research project should be able to question the mechanisms used to develop, review and implement research protocols (Institute of Medicine, 2003). Research participants also need to be aware of their own responsibilities to comply with the protocol in order to prevent harm or invalidate the study. While the issues for communication are broadly similar for microbial challenge and other studies, it is worth emphasising that there may be a general need for more structured framework for participants to provide feedback. For example, a 'Research Day' (Institute of Medicine, 2003) in which past and current participants are invited to share views on their research experience may be a proactive way to gain input on institutional processes and policies.

Chapter eight - *Consent and confidentiality*

Respect for autonomy of potential research participants

- 8.1 Respecting the autonomy of potential research participants has implications for both the consent procedure and confidentiality. For consent to be valid, the potential participant must be properly informed about those issues relevant to making a decision, and free from any coercion to take part. The potential participant should have the capacity to understand the relevant information and to make a decision. Respecting autonomy also requires that personal information should not normally be shared without the explicit consent of the person to whom it relates.
- 8.2 The involvement of competent adults in medical research in the UK is governed mainly by the common law concept of consent. In brief, this means that the potential research subject should be given information about the nature and purpose of the research procedures, the fact that this is motivated by a research intention and the advantages and disadvantages of taking part in the research. It is likely that, in the case of research, the courts would demand a higher level of information concerning risk than they would in the case of medical treatment. This would be particularly so in the case of non-therapeutic research. The researcher must take steps to ensure that the subject understands the information: for example, the design of the research in broad terms, including the use of randomisation, when made.
- 8.3 The provision of information must be sufficiently flexible to take account of the varying needs and levels of understanding of different subjects; in view of the complex nature of challenge studies, information sheets may be more detailed than for many other clinical research protocols. Some centres evaluate understanding by the subjects of information supplied by means of a written test; in the event of a legal case, it is quite possible that the volunteer would dispute his/her level of understanding so that the information ought to be

reviewed by an expert third party and, a consumer/lay person to ensure that it is appropriate and clearly written in a non-technical language. One issue for further discussion, therefore, is the extent to which an audit of competence and understanding of consent procedures should be formalised and made obligatory.

- 8.4 The general principles and practice of informed consent for microbial challenge studies do not differ from those applied to other forms of medical research (see Chapter 7 for specific points). It is imperative that the consent procedures, and ethical review process more generally, focus on subject safety rather than institutional protection against liability. The ICH GCP Guidelines stipulate that freely given informed consent should be obtained from every subject prior to participation (E6 2.9) and provides detailed advice on how the information presented to subjects should be set out, acknowledged and updated (E6 4.8) as currently practised by ethics committees in the UK. In general, information supplied in microbial challenge studies should follow the current ICH guidelines and it should be made clear that there is unlikely to be a foreseeable health benefit to the volunteer associated with participating in the trial.
- 8.5 Further discussion of issues is provided in the standard texts on volunteer studies (Kennedy and Grubb, 2000; Doyal and Tobias, 2001). Detailed guidance on informed consent procedures and subject information for research to be performed under the aegis of the ECTD was published by the European Union (European Commission, 2003) and this will also be relevant to microbial challenge studies.

Use of tissue samples

- 8.6 In November 2004 the Human Tissue Act that regulates the removal, storage and use of human bodies, organs and tissue for research and other purposes received Royal Assent¹. The main parts

¹ Copies of the Act are available from: <http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm>

of this act are expected to come into force in April 2006. In addition, there are also many guidelines relating to the use of human tissues for research, surveillance or other purposes (e.g. MRC, Department of Health, Royal College of Pathologists etc.). One area for consideration relates to the ability to use residual tissue samples for purposes other than the primary purpose for which consent for the sample was obtained. This should not normally be the case in microbial challenge studies, where explicit informed consent to the study procedures, including taking of tissue samples for this purpose, can be sought at the outset. In line with the ICH guidelines (E6 1.28 and 4.8.10) there must be detail provided of the tests to be performed and their purpose, and possible consequences. There should be explanation and consent for specific actions such as retention of tissues after study completion or transfer to other sites.

8.7 However, it may not always be possible to specify all tests at the outset. The purpose of the study may, for example, be to improve understanding of the pathogenic processes that accompany or follow infection, including an understanding of the effects of these processes on the nature of the infecting agent. Under these circumstances, it might be difficult to formulate a study hypothesis and anticipate the range of tests that might eventually be performed on the tissues even many years later. As technological advances are made (e.g. use of PCR techniques to amplify DNA), future application of new tests on stored tissues could be extremely valuable. A more generic consent to allow application of novel tests on stored samples obtained from microbial challenge studies could, therefore, be considered by the investigator. For example, a precedent now exists for samples obtained in vaccine trials. Whilst not explicitly set out in the Human Tissue Act, the Minister provided reassurance during the Bill's passage through Parliament that the consent required under the Act need not be onerous - particularly that it could be broad and durable². Further clarification of this is expected to be provided in Codes of Practice to be issued by the Human Tissue Authority.

8.8 The UK Vaccine Evaluation Consortium uses a generic consent statement, *'I consent to the use of*

any residual samples being used within the UK Vaccine Evaluation Consortium, once made anonymous, to improve the understanding of vaccines and how they work. I understand that this is optional and that I can still take part in the study if I do not give my consent for this.' This statement allows the use of residual tissue samples for tests other than those specified in the original clinical trial protocol in an anonymous manner. Such consent has already proved valuable for conducting antibody persistence studies of vaccines opportunistically received by the study cohorts prior to recruitment into the trial. The Human Tissue Act 2004 does not require consent for the use of tissue for REC approved research, providing the tissue is anonymised by the researcher.

8.9 There is one other issue to consider. Challenge studies could result in the identification of intellectual property (IP) associated with material relating to the challenge microbe or host immune responses (for example, an unusual variant or mutant derived from the challenge strain or an antibody in response to the challenge procedure) that might be subject to the filing of a patent. The ownership of this IP and rights to its exploitation should be made explicit as part of the consent process. As emphasised by the MRC 1999 guidelines, research participants would not normally be entitled to a share of any profits that might ensue. Despite this, participants are usually willing to donate tissues for research that may lead to commercialisation (Jack and Womack, 2003).

Confidentiality

8.10 Microbial challenge studies raise the same issues for confidentiality and privacy as do other types of medical research. In line with current ICH GCP guidelines, study information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification (E6 2.10) and protected respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s) (E6 2.11). Systems with procedures that assure the quality of every aspect of the study should be implemented (E6 2.13).

² The Minister also noted that research ethics committees may, in individual research projects, sometimes ask for specific consent. See Hansard 22 July 2004.

Chapter nine - *Legal issues*

9.1 The present paper has attempted to identify best current practice by cross-referring to other documents and recognises that the clinical research environment is changing in consequence of the implementation of the ECTD. Researchers have responsibility for ensuring that research is carried out to both the highest scientific and ethical standards. These responsibilities are shared with - but cannot be delegated to - research ethics committees and the scientific peer review procedures. Researchers also have a responsibility to ensure that the research peer and ethical review processes have the necessary, specialised expertise and authority.

Issues for damages

9.2 In the absence of a specific regulatory framework for volunteer challenge studies, the agreement between investigator and research participant would be subject to common law, with the participant entitled to claim damages for any harm that ensued, if it could be proven that the investigator had been negligent. In the event of a claim for negligence, interpretation of critical issues (discussed in the previous Sections) is likely to be judged against best practice according to prevailing expert opinion. To summarise, key issues that are likely to be the focus of legal proceedings include:

- were the investigator and others involved in running the study appropriately qualified to do so? While clinical researchers are empowered to carry out procedures on humans as part of their qualification, it would be appropriate to ensure that they could be demonstrated to be 'expert' in their field.
- were the risks estimated on a sound basis? A thorough review of pre-existing knowledge and a written risk assessment should be in place at the outset of the study. Third party expert endorsement would be advisable.
- were the risks to the volunteer appropriate considering the circumstances? The consensus of previous debate has been that healthy

volunteer studies should not involve more than minimal risk of harm. It would, therefore, be difficult to maintain that posing 'greater than minimal harm' was acceptable.

- were the procedures undertaken to a sufficiently high standard? Important factors are the training of staff (and documentation of that training) and the quality/reliability of equipment and materials used.
- were appropriate consent procedures followed (see Chapter 8)?

Indemnity

9.3 The indemnity issues surrounding a microbial challenge study are similar to those relating to other clinical research. The international experience in compensation for research-related injury (including no-fault guidelines of the UK Association of British Pharmaceutical Industry) was reviewed recently by the Institute of Medicine (2003). It would appear unwise to proceed with such a study without insurance or indemnity to cover any liability. Normally, the host institution would provide indemnity for an investigator and the necessary arrangements have to be established locally. In view of the points made previously, a host institution might balk at providing such indemnity unless convinced that the investigator is adhering to best practice for clinical trials and the institution should therefore have a process to scrutinise such research. The investigator should determine the specific legal requirements for either no-fault or negligence insurance. The type and level of indemnity and insurance, and its consequences, should be clearly defined in the information sheet for the volunteer (COREC provides sample text).

9.4 As with some of the other topics discussed in this paper, it would aid rational analysis of the issues relating to injury and attribution to research procedures if there were a central database of such incidents, set into context of the total volume of research undertaken.

Appendix 1 - *Checklist of ethical issues that researchers and ethics committees need to consider*

Consent

- Competent
- Informed
- Voluntary

Confidentiality

- Patient contact details
- Information from medical records
- Research data and results

Risk of harm to patients

- Physical
- Psychological
- Therapeutic/non-therapeutic research

Value and quality of the research

- Are the aims worthwhile?
- Is the methodology appropriate to the aims?
- Are the outcomes clinically significant
- Are the outcomes patient centred?

Justice

- Are the inclusion and exclusion criteria appropriate?

Appendix 2 - *Abbreviations and acronyms*

BMJ	British Medical Journal	GMO	Genetically Modified Organism
CIOMS	Council for International Organisations of Medical Science	GMP	Good Manufacturing Practice
COREC	Central Office for Research Ethics Committees	ICH	International Conference on Harmonisation
COSHH	Control of Substances Hazardous to Health Regulations	IP	Intellectual Property
CTC	Clinical Trials Certificate	JAMA	Journal of the American Medical Association
CTX	Clinical Trials Exemption	LREC	Local Research Ethics Committee
DEFRA	Department of the Environment, Food and Rural Affairs	MHRA	Medicines and Healthcare Products Regulatory Authority
ECTD	European Clinical Trials Directive	MRC	Medical Research Council
EMA	European Medicines Evaluation Agency	MREC	Multicentre Research Ethics Committee
FDA	Food and Drugs Administration	NEAC	National Expert Advisory Committee
GCP	Good Clinical Practice	PCR	Polymerase Chain Reaction
GLP	Good Laboratory Practice	R&D	Research and Development
		RCP	Royal College of Physicians
		SAE	Serious Adverse Event
		WMA	World Medical Association

Appendix 3 - Working and Review Group Membership

Working Group

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With support from the Academy's Executive Director (Mrs Mary Manning), Senior Policy Advisor (Dr Robin Fears), Policy Officer (Mr Laurie Smith) and in consultation with the Officers of the Academy.

Appendix 4 - *Work plan*

In 2002 the Academy of Medical Sciences organised a meeting in Oxford to provide a forum for critical discussion of the risks, benefits and conduct of microbial challenge studies of human volunteers, with particular emphasis on the role of such studies to facilitate the research and development of vaccines. Subsequently, the Academy Council convened a Working Group to consider the issues further and prepare a position paper on the proper conduct of such studies.

The Working Group held meetings between March 2003 and May 2004. Working Group members, supported by the research capacity of the secretariat, provided evidence, analysis of issues and strategic prioritisation. A draft report was circulated to key stakeholders for consultation between February and April 2004. A wider general call for evidence was also issued between July and August 2004. The Academy's review procedure was initiated in August 2004 and completed in January 2005 with final copy of the report being submitted for publication in July 2005.

Appendix 5 - Respondents to the consultation

The Academy would like to thank the following individuals for responding to the Academy's consultation with stakeholders between February and April 2004:

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